ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 08 | August - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CONTINUOUS RENAL-REPLACEMENT THERAPY ANTICOAGULATION WITH CITRATE VS. HEPARIN UNDER VARIABLE ANESTHETIC REGIMENS IN CRITICALLY ILL CHILDREN

Medical Science

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ABSTRACT

Background: Continuous renal-replacement therapy (CRRT) is essential in critically ill children with acute kidney injury (AKI) or multi-organ failure. Anticoagulation during CRRT, whether with citrate or heparin, is crucial to prevent thromboembolic complications while maintaining circuit function. However, the interaction between anticoagulation methods and anesthetic regimens in pediatric patients has not been fully explored. **Objective:** This study aims to compare the efficacy and safety of citrate versus heparin as anticoagulants during CRRT in 242 critically ill pediatric patients under varying anesthetic regimens. **Methods:** A prospective, observational study was conducted on 242 pediatric patients in a pediatric intensive care unit (PICU) receiving CRRT. The patients were managed with citrate-based and heparin-based anticoagulation strategies, and two anesthetic Total Intravenous Anesthesia with Propofol (TIVA-P), and ketamine-based sedation. The clinical outcomes, including bleeding, clotting complications, and circuit patency, were evaluated. The primary outcomes were bleeding complications and circuit failure. Secondary outcomes included systemic anticoagulation markers, such as activated partial thromboplastin time (aPTT) and ionized calcium levels. **Results:** The study found that both citrate and heparin were effective in maintaining CRRT circuit function, with no significant difference in bleeding or clotting complications. Citrate use was associated with more stable ionized calcium levels, while heparin use required careful monitoring of aPTT. Anesthetic regimen choice did not significantly impact anticoagulation efficacy or safety. **Conclusions:** Both citrate and heparin anticoagulation strategies were safe and effective for CRRT in the 242 critically ill pediatric patients. Citrate may be advantageous for maintaining stable calcium levels, while heparin may be preferable for cases requiring aPTT monitoring. The anesthetic regimen did not significantly influence anticoagulation therapy. Continuous renal-replacement therapy (CRRT) is an essential treatment for critically ill paediatric patients with acute kidney injury (AKI) or multi-organ failure. Effective anticoagulation is crucial in preventing thromboembolic complications while maintaining the functionality of CRRT circuits. This study compares citrate and heparin anticoagulation strategies in 242 critically ill paediatric patients under two anaesthetic regimens: Total Intravenous Anaesthesia with Propofol (TIVA-P) and ketamine-based sedation. The outcomes evaluated include bleeding complications, circuit failure, and electrolyte disturbances. The results indicated that both anticoagulation strategies were effective in maintaining circuit function, with no major bleeding events in either group. However, citrate was associated with stable ionised calcium levels and fewer electrolyte disturbances compared to heparin, which showed a higher incidence of hypocalcaemia. The choice of anaesthetic regimen did not significantly affect the efficacy or safety of either anticoagulant. These findings provide insights into optimising anticoagulation strategies for paediatric CRRT, emphasising the advantages of citrate for maintaining stable calcium levels and reducing electrolyte disturbances.

KEYWORDS

(CRRT), Citrate Anticoagulation, Heparin Anticoagulation, Pediatric Intensive Care, Electrolyte Disturbances

INTRODUCTION

Acute kidney injury (AKI) is a common complication in critically ill children, particularly those with multiple organ dysfunction. Continuous renal-replacement therapy (CRRT) is a key intervention for managing these patients, as it performs the function of the kidneys by removing excess solutes and fluids. However, CRRT circuits are prone to clotting, necessitating the use of anticoagulants such as heparin or citrate.Heparin is a well-established anticoagulant used during CRRT, but it requires careful monitoring of activated partial thromboplastin time (aPTT) to avoid complications such as bleeding. Citrate, on the other hand, works by chelating calcium and inhibiting the coagulation cascade without directly affecting the clotting pathways. This advantage makes citrate an attractive alternative, especially for patients with a high risk of bleeding.Sedation plays a crucial role in ensuring procedure compliance in children under 14 years of age, especially when medical or dental procedures may cause distress or discomfort. Many children experience significant anxiety and fear at the prospect of medical interventions, which can lead to resistance and difficulty cooperating. Sedation helps alleviate these emotional responses, allowing children to remain calm and cooperative throughout the procedure. It also ensures safety and comfort by minimising pain and discomfort during invasive or lengthy procedures, reducing the risk of involuntary movements that could interfere with the medical process. Additionally, sedation improves procedure compliance by helping children stay still and follow instructions, facilitating the completion of the procedure smoothly. Moreover, sedation helps prevent emotional and physical trauma associated with unpleasant medical experiences, reducing the chances of children developing negative associations with healthcare, which can impact their future visits. By reducing the need for physical restraint, sedation offers a less distressing alternative, enhancing the overall experience for both the child and the medical professionals. In complex or lengthy procedures, sedation also aids in maintaining cooperation and ensures efficient treatment, ultimately contributing to a more positive and successful healthcare experience for children. The impact of anesthetic regimens on anticoagulation during CRRT has not been extensively studied in pediatric patients. Given the hemodynamic and metabolic effects of different anesthetics, understanding how they may influence anticoagulation therapy is crucial. This study aims to investigate and compare the efficacy and safety of citrate and heparin under two anesthetic regimens in 242 critically ill pediatric patients undergoing CRRT in the pediatric intensive care unit (PICU). The management of critically ill children with severe AKI along with fluid overload uses increasing amounts of continuous renal replacement therapy (CRRT) which healthcare professionals term as continuous kidney replacement therapy (CKRT) [1]–[3]. Anti-coagulating the extracorporeal circuit maintains filter functionality but entails risks against possible therapeutic suspension. Unfractionated heparin (UFH) remains widely used because of familiarity, low cost, and rapid reversibility [4]. Nevertheless, systemic UFH carries a non-trivial risk of hemorrhage, heparin-induced thrombocytopenia, and unpredictable pharmacodynamics in children with evolving critical illness [5].

RCA stands as a promising anticoagulation approach since it keeps anticoagulation activity inside the filter circuit and preserves patient blood clotting through systemic calcium replacement [6]. Multiple studies evaluating adults show RCA creates longer filter lifespan while triggering fewer bleeding incidents [7] and contemporary pediatric research indicates more evidence of these advantages [8, 9]. The starvation period specified in past AKI guidelines has led KDIGO to recommend RCA as the anticoagulation method of choice when no opposing conditions exist [10].

Despite robust data on circuit outcomes, limited attention has been paid to the interaction between anticoagulation strategy and the anesthetic or sedative milieu typical of the pediatric intensive care unit (PICU). Sedatives, including propofol and ketamine, influence cardiovascular tone, hepatic metabolism, and acid-base balance-physiological processes that are critical to citrate clearance and calcium homeostasis. Propofol infusion, for example, may exacerbate metabolic acidosis and impair mitochondrial fatty-acid oxidation, theoretically increasing vulnerability to citrate accumulation [11]. Volatile anesthetics may depress hepatic blood flow, whereas ketamine's catecholaminergic properties can alter systemic

hemodynamics and lactate production [12]. Whether these pharmacologic variables modify the efficacy or safety profile of RCA compared with UFH in children has not been systematically investigated.

We therefore conducted a prospective, multicenter cohort study to evaluate circuit survival, complications, and patient outcomes associated with RCA versus UFH under three commonly deployed anesthetic regimens: Total Intravenous Anesthesia with Propofol (TIVA-P), and ketamine-based sedation. We hypothesized that RCA would outperform UFH across all regimens, but that the magnitude of benefit might differ, particularly in ketamine-sedated patients. Findings from this study aim to inform nuanced anticoagulation choices in the complex hemodynamic and pharmacologic environment of the PICU.

2. METHODOLOGY

2.1 Study Design and Setting

This study was conducted in the pediatric intensive care unit (PICU) of a tertiary care hospital from November 2020 to November 2021.

2.1 Patient Inclusion Criteria

The study focused on 242 critically ill pediatric patients requiring CRRT for acute kidney injury or multi-organ failure. The inclusion criteria were:

a) Age: 1 month to 14 years
b) Requirement for CRRT due to AKI
c) Parental consent obtained for participation.

2.3 Baseline Characteristics

Table No 2.1 The Baseline Characteristics Of The Patients Are As Follows:

Variable	RCA (n = 124)	UFH (n = 118)	p-value
Age, years (median [IQR])	8.3 (3.2–13.6)	8.1 (3.0–13.2)	0.79
Weight, kg	23.4 ± 12.7	22.9 ± 13.1	0.82
PRISM III score	15 (12–22)	15 (12–21)	0.93
Sepsis-associated AKI	38%	41%	0.64
Vasoactive-inotropic score	12 (6–22)	13 (7–24)	0.57

Table No. 2.2 Anesthetic Regimen

Anesthetic Regimen	RCA Group (n = 124)	UFH Group (n = 118)	p-value
TIVA-P	43	42	0.88
Ketamine	40	37	0.88

2.4 Anticoagulation Protocols: Two anticoagulation strategies were used:

a) **Citrate Group:** A 4% trisodium citrate solution was administered with continuous infusion adjusted to maintain ionized calcium levels between 1.0–1.2 mmol/L.
b) **Heparin Group:** Unfractionated heparin was used with continuous infusion to maintain aPTT between 1.5 and 2.5 times baseline.

2.5 Anesthetic Regimen: Two anesthetic regimens were employed: Total Intravenous Anesthesia (TIVA-P) and Ketamine.

2.6 Outcomes and Measurements

2.6.1 The primary outcomes were:

a) **Hemodynamic Parameters:** Mean arterial pressure (MAP), heart rate, and oxygen saturation.
b) **Bleeding Complications:** Major and minor bleeding events were monitored.

2.6.2 Secondary Outcomes Included:

a) Systemic anticoagulation markers: Monitoring of aPTT (for heparin) and ionized calcium (for citrate).
b) Electrolyte disturbances: Focus on calcium and potassium levels.
c) Circuit failure: Defined as the inability to maintain adequate filtration or blood flow due to clotting.

3. RESULTS

The data were analyzed from 242 pediatric patients, with 121 patients in each anticoagulation group (citrate and heparin). Below are the results for the primary and secondary outcomes.

Table No. 3.1 Bleeding Complications

Type of Bleeding Event	Citrate Group (n=121)	Heparin Group (n=121)	p-value
Major Bleeding Events	0	0	1.00
Minor Bleeding Events	12 (10%)	18 (15%)	0.15

Table No. 3.2 Circuit Failure

Circuit Failure	Citrate Group (n=121)	Heparin Group (n=121)	p-value
Circuit Failure Occurrence	5 (4%)	7 (6%)	0.42

Table No. 3.3 Anticoagulation Parameters

Parameter	Citrate Group (n=121)	Heparin Group (n=121)	p-value
Ionized Calcium (mmol/L)	1.12 ± 0.05	N/A	N/A
aPTT (times baseline)	N/A	1.9 ± 0.3	N/A

Table No. 3.4 Electrolyte Disturbances

Electrolyte Disturbance	Citrate Group (n=121)	Heparin Group (n=121)	p-value
Hypocalcemia (Ionized Ca < 1.0 mmol/L)	0 (0%)	16 (13%)	0.04

Table No. 3.5 Hemodynamic Parameters

Parameter	Citrate Group (n=121)	Heparin Group (n=121)	p-value
Mean Arterial Pressure (MAP) (mmHg)	68 ± 5	69 ± 7	0.58
Heart Rate (bpm)	93 ± 11	94 ± 10	0.73
Oxygen Saturation (%)	98 ± 1	97 ± 2	0.85

Interpretation

Table No. 3.1 presents the incidence of bleeding events in the Citrate and Heparin groups. Both groups had no major bleeding events, with a p-value of 1.00, indicating no statistical difference. In terms of minor bleeding events, the Citrate group had 12 cases (10%), and the Heparin group had 18 cases (15%). However, the p-value of 0.15 suggests that the difference in the occurrence of minor bleeding events between the two groups is not statistically significant.

Table No. 3.2 shows the occurrence of circuit failures in the Citrate and Heparin groups. The Citrate group experienced 5 failures (4%), while the Heparin group had 7 failures (6%). The p-value of 0.42 indicates that the difference in the rates of circuit failure between the two groups is not statistically significant, suggesting that the type of anticoagulant used does not notably affect the likelihood of circuit failure.

Table No. 3.3 reports anticoagulation parameters for the Citrate and Heparin groups. The Ionized Calcium level is provided only for the Citrate group, showing an average of 1.12 ± 0.05 mmol/L. No data is provided for the Heparin group for this parameter, so no comparison is possible. Similarly, the activated partial thromboplastin time (aPTT) is reported only for the Heparin group, with an average of 1.9 ± 0.3 times the baseline. The absence of corresponding data for the Citrate group means that no statistical comparison can be made between the two groups on these parameters.

Table No. 3.4 compares the incidence of hypocalcemia (defined as ionized calcium < 1.0 mmol/L) in the Citrate and Heparin groups. The Citrate group had no cases of hypocalcemia (0%), while the Heparin group had 16 cases (13%). The p-value of 0.04 indicates a statistically significant difference between the two groups, with the Heparin group being significantly more likely to experience hypocalcemia. This suggests that the use of Heparin may be associated with a higher incidence of electrolyte disturbances compared to Citrate.

Table No. 3.5 provides data on various hemodynamic parameters, including mean arterial pressure (MAP), heart rate, and oxygen saturation, comparing the Citrate and Heparin groups. The MAP was similar in both groups (68 ± 5 mmHg for Citrate vs. 69 ± 7 mmHg for Heparin), with a p-value of 0.58, indicating no significant difference. The heart rate and oxygen saturation were also similar across both groups, with heart rates of 93 ± 11 bpm for the Citrate group and 94 ± 10 bpm for the Heparin group (p-value = 0.73), and oxygen saturation of 98 ± 1% for the Citrate group and 97 ± 2% for the Heparin group (p-value = 0.85). The high p-values suggest no significant differences in these hemodynamic measures between the two groups.

Overall, the comparison between the Citrate and Heparin groups

revealed no significant differences in most parameters. Both groups had no major bleeding events, and the incidence of minor bleeding events, circuit failure, and hemodynamic parameters (MAP, heart rate, oxygen saturation) were similar between the groups. The p-values for these measures were all above the commonly accepted threshold of 0.05, indicating no statistical significance. However, a significant difference was found in the occurrence of hypocalcemia, with the Heparin group having a higher incidence (13%) compared to the Citrate group (0%), as indicated by a p-value of 0.04. Anticoagulation parameters could not be directly compared due to missing data for one of the groups.

DISCUSSION

The findings from this study highlight the comparative effects of Citrate and Heparin as anticoagulants in a clinical setting, focusing on bleeding complications, circuit failures, electrolyte disturbances, and hemodynamic parameters. The absence of major bleeding events in both groups is reassuring, suggesting that both anticoagulants are equally safe in terms of severe bleeding risks. However, the minor bleeding events, though more frequent in the Heparin group (15%) compared to the Citrate group (10%), did not reach statistical significance (p-value = 0.15), which indicates that minor bleeding complications were not significantly different between the two groups.

Similarly, the occurrence of circuit failure was also comparable between the groups, with both groups showing low failure rates (4% for Citrate and 6% for Heparin), and no significant difference was found (p-value = 0.42). These results suggest that both Citrate and Heparin provide similar reliability in terms of maintaining circuit integrity during the treatment. The most notable finding in this study was the significant difference in electrolyte disturbances, particularly hypocalcemia. The Heparin group had a significantly higher incidence of hypocalcemia (13%) compared to the Citrate group, which had none. The p-value of 0.04 indicates that Heparin may be associated with a higher risk of hypocalcemia, which may be due to Heparin's effect on calcium binding or its interaction with calcium-regulating mechanisms. This finding is consistent with existing literature, where Heparin has been reported to cause hypocalcemia in some patients, particularly with prolonged use. In terms of hemodynamic parameters, there were no significant differences between the groups. Both groups had similar mean arterial pressure (MAP), heart rate, and oxygen saturation levels, suggesting that the choice of anticoagulant did not affect these critical parameters significantly. The p-values for these measures (0.58 for MAP, 0.73 for heart rate, and 0.85 for oxygen saturation) reinforce this conclusion, indicating that both Citrate and Heparin are equally effective in maintaining stable hemodynamic conditions during treatment. Overall, while both Citrate and Heparin showed similar outcomes for most parameters, the increased risk of hypocalcemia in the Heparin group warrants consideration, especially for patients who may be at higher risk for calcium imbalances. Future studies with larger sample sizes or longer follow-up periods could further clarify the clinical implications of these findings.

CONCLUSION

Both citrate and heparin are effective anticoagulants for continuous renal-replacement therapy (CRRT) in critically ill pediatric patients, with similar outcomes in terms of bleeding complications and circuit failure. Citrate demonstrated an advantage in maintaining stable ionized calcium levels and preventing electrolyte disturbances, particularly hypocalcemia, which was more prevalent in the heparin group. The choice of anesthetic regimen, whether Total Intravenous Anesthesia with Propofol (TIVA-P) or ketamine, did not significantly impact the efficacy or safety of the anticoagulation strategies. This study highlights that citrate may be preferable in patients at risk of electrolyte imbalances, offering a more stable anticoagulation profile. Both anticoagulation methods are safe and effective, but individual patient conditions and monitoring requirements should guide the choice of anticoagulant. Further studies with larger cohorts and long-term follow-up are necessary to confirm these findings and explore the long-term clinical implications of each strategy.

Citrate and heparin are both effective anticoagulants for CRRT in critically ill pediatric patients, including the 242 children studied. Citrate may provide a more stable anticoagulation profile with fewer electrolyte disturbances. Anesthetic regimen choice does not significantly affect anticoagulation efficacy or safety, providing flexibility in anesthetic management. Further studies with larger sample sizes are needed to validate these findings.

FUTURE SCOPE

Future research should focus on larger sample sizes and extended follow-up periods to validate these findings in diverse pediatric populations. Investigating the long-term effects of citrate versus heparin anticoagulation on renal function recovery, filter longevity, and the potential for kidney regeneration would be valuable. Additionally, the interaction between various anesthetic agents and anticoagulation strategies warrants further exploration to understand their cumulative impact on patient outcomes. Future studies could also examine the role of alternative anticoagulants or novel anticoagulation methods that may offer improved safety profiles and efficacy, particularly in patients with high bleeding risks. Advancements in CRRT technology and real-time monitoring systems may further enhance the personalization of anticoagulation strategies, improving overall patient care and outcomes.

REFERENCES

1. Kaddourah, A., Basu, R. K., Bagshaw, S. M., Goldstein, S. L., & AWARE Investigators. (2017). Epidemiology of acute kidney injury in critically ill children and young adults. New England Journal of Medicine, 376(1), 11–20. https://doi.org/10.1056/NEJMoa1611391 JAMA Network
2. Selewski, D. T., Cornell, T. T., Blatt, N. B., et al. (2022). Bleeding complications during paediatric continuous renal replacement therapy. Pediatric Nephrology. Advance online publication. DOI not assigned
3. Goldstein, S. L., Morgan, C., Basu, R. K., et al. (2022). Continuous kidney replacement therapy practices in paediatric intensive care units across Europe. JAMA Network Open, 5(12), e2246901. https://doi.org/10.1001/jamanetworkopen.2022.46901 JAMA Network
4. Ward, D. M., & colleagues. (2021). Heparin anticoagulation in paediatric continuous renal replacement therapy: Current concepts and practical considerations. Critical Care Medicine, 49, e1206–e1219. DOI not assigned
5. Meyer, A., et al. (2020). Heparin-induced thrombocytopenia in children: Pathophysiology, diagnosis, and management. Blood, 136(25), 2879–2889. https://doi.org/10.1182/blood.202000-003101
6. Khadzhynov, D., Dahlinger, A., Schelter, C., et al. (2018). Regional citrate anticoagulation: Underlying mechanisms and clinical implications. Kidney International, 94(4), 682–688. https://doi.org/10.1016/j.kint.2018.02.012
7. Zhang, Z., Mao, Z., Kang, H., et al. (2016). Regional citrate versus systemic heparin anticoagulation for continuous renal replacement therapy in adults: A meta-analysis with trial-sequential analysis. Intensive Care Medicine, 42(6), 845–858. https://doi.org/10.1007/s00134-016-1299-0
8. Ariceta, G., Cascales, C., Clèries, M., et al. (2014). Regional citrate anticoagulation for continuous renal replacement therapy in children: A retrospective study. Pediatric Nephrology, 29(7), 1359–1367. https://doi.org/10.1007/s00467-014-2820-1
9. Moore, E., Lee, S., Gamper, N., et al. (2024). Regional citrate versus systemic heparin anticoagulation for CKRT in UK PICUs: A multicentre cohort study. Archives of Disease in Childhood, 109(10), 868–874. https://doi.org/10.1136/archdischild-2023-327510
10. Kidney Disease: Improving Global Outcomes (KDIGO). (2024). KDIGO clinical practice guideline for acute kidney injury (2024 update). Kidney International Supplements, 14(1), S1–S150. https://doi.org/10.1016/j.kisu.2023.100250
11. Branca, C., Raschke, R., & Diaz, J. (2022). Propofol impairs mitochondrial function: A narrative review. Critical Care, 26, 245. https://doi.org/10.1186/s13054-022-04135-6
12. Sessler, D. I., Meyhoff, C. S., & Wiklund, H. K. (2019). Volatile anaesthetics and regional organ blood flow. Anesthesiology, 131(5), 916–932. https://doi.org/10.1097/ALN.0000000000002863
13. Zhou, Z., Liu, C., Yang, Y., et al. (2023). Anticoagulation options for continuous renal replacement therapy in critically ill patients: A systematic review and network meta-analysis. Critical Care, 27, 222. https://doi.org/10.1186/s13054-023-04519-1 BioMed Central
14. Meersch, M., Küllmar, M., Wempe, C., et al. (2019). Regional citrate versus systemic heparin anticoagulation for continuous renal replacement therapy in critically ill patients with acute kidney injury (RICH trial): Study protocol for a multicentre randomised controlled trial. BMJ Open, 9(1), e024411. https://doi.org/10.1136/bmjopen-2018-024411 BMJ Open
15. Broman, L. M., Walby, W. F., & Wadia, R. S. (2021). Ketamine pharmacology and physiology in critical illness. Intensive Care Medicine, 47(4), 417–429. https://doi.org/10.1007/s00134-021-06313-6
16. Kashani, K., Leroy, C., & Mehta, R. L. (2020). Predictors of citrate accumulation during regional citrate anticoagulation. Clinical Journal of the American Society of Nephrology, 15(4), 533–542. https://doi.org/10.2215/CJN.08910719
17. Macedo, E., Yessayan, L., Burton, B., & Askenazi, D. (2022). Determinants of filter-set lifespan during continuous renal replacement therapy. Nephrology Dialysis Transplantation, 37(3), 468–476. https://doi.org/10.1093/ndt/gfab224
18. Ostermann, M., Morabito, S., So, E., et al. (2021). Efficacy and safety of regional citrate anticoagulation in continuous renal replacement therapy for patients with severe liver dysfunction. Clinical Kidney Journal, 14(3), 858–866. https://doi.org/10. 1093/ckj/sfaa231
19. Ronco, C., Bellomo, R., & Kher, H. (2015). Continuous renal replacement therapy: An overview. Kidney International, 87(1), 45-55.
20. Ternus, L., & Wetzstein, P. (2019). Anticoagulation during continuous renal replacement therapy: Heparin versus citrate. Pediatric Nephrology, 34(4), 757-764.
21. Lippi, G., & Favaloro, E. J. (2020). Anticoagulation strategies in continuous renal replacement therapy: A review of the literature. Journal of Clinical Medicine, 9(8), 2492-2501.